Formamidine Reactions

by E. L. Griffin

1913

A Thesis Presented to the Faculty of the Graduate School of the University of Kansas. In partial fulfillment of the Requirements For the Degree of Master of Science.

FORMAMIDINE REACTIONS.

On the Synthesis of Isoxazolon, Isoxazol, Cyanacetic and Benzoyl acetic acid derivatives.

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May 15, 1913.

PREFACE.

This thesis represents work done in the organic chemistry research laboratory during the years 1911-1912 and 1912-1913. Many of the preparations were made by Dr. F.B. Dains and in all cases the work was under his close supervision. The analyses were all by the author.

I wish to express my gratitude to Dr. Dains for the continued assistance and encouragement which has made this paper possible.

FORMAMIDINE REACTIONS.

In papers published by Dr. F.B. Davis,[1] and by Dr. F.B. Davis and E.W. Brown,[2] it has been shown that substituted formamidines react with certain compounds containing methylene hydrogen, these reactions having been particularly studied in the cases of malonic ester, aceto acetic ester, acetylacetone, and cyan-acetic ester, It was found that the H of the methylene group together with the :NR of the formamidine splits off as an amine, the :CH.NHR joining to the remainder of the first compound. The reaction is, then, as follows, where X and Y are two negative groups and R an alkyl group.

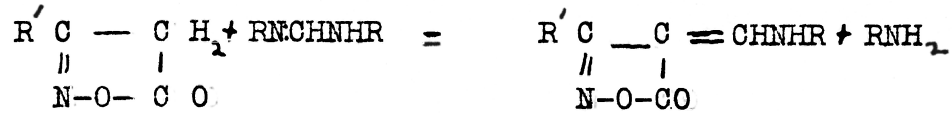
$$RN{:}CHNHR + H_2C{\cdot}X{\cdot}Y = RNHCH{:}CXY + RNH_2$$

It usually takes place to best advantage when the two reacting substances are heated. Some, such as di-o-phenetdyl formamidine and acetoacetic ester, will react at the temperature of the boiling water bath. Others require various temperatures up to about 160°. The reaction usually takes place the more easily, the more negative the groups next to the CH_2 groups are, that is, the more acid the methylene hydrogen is.

In this case the reactions of some of the ring compounds containing methylene hydrogen were studied. The isoxazolons are compounds which answer this description and can be obtained in quantities to use. Following the same reactions as those

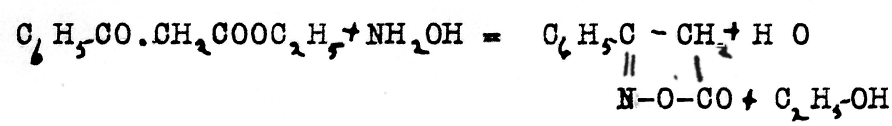
(1) Ber. 35, 2496 (2) J Am. Chem. Soc. 31, 1148.

given above the following results would be obtained:



PHENYL ISOXAZOLON REACTIONS.

Phenyl isoxazolon 1) was made by dissolving benzoyl acetic ester in alcohol, adding to this solution a concentrated solution of one mol of hydroxylamine hydrochloride in water, and then heating the whole on a water-bath for a half hour. It is then set aside to cool and let the phenyl isoxazolon crystalize out, after which it can be filtered off, dried and recrystalized from alcohol as a white crystaline compound which melts at 152.° The yield was 15 gms. from 20 gms of the ester.



Phenyl isoxazolon is a fairly strong acid, one hydrogen of the CH_2 group being replacable by a metal. The salts with several metals have been prepared and from the silver salt and the alkyl iodides, 2) esters have been obtained.

1) Ber. 24. 140. Claisen

2) Ann. 266. 33

Many of the other reactions of methylene hydrogen have also been shown and there-fore it was to be expected that it would react

with the formamidines.

4-Anilido methylene-3-phenyl-5-isoxaxolon.

When equal molecular amounts of diphenyl formamidine and phenyl isoxazolon were heated in an oil bath at 120° for one hour, they formed a liquid which on cooling solidified. From this solid a yellow compound was crystalized out by the use of alcohol and then recrystalized from ethyl-acetate. It came out in beautiful, yellow, rhombic, crystals which melt at 145°. The alcohol residue from which the product was crystalized was evaporated down and then treated with benzoyl chloride and sodium hydroxide solution. A large amount of benzanilid which melted at 160° was obtained. The reaction was probably as follows:

$$C_6H_5C(=N{-}O{-}CO)CH_2 + C_6H_5NCHNHC_6H_5 = C_6H_5C(=N{-}O{-}CO){-}C(=CHNHC_6H_5){-}C_6H_5NH_2$$

A kjeldahl analysis for nitrogen gave the following results:

Substance	.2311 gm.	.3252 gm	Factor $\frac{HCl}{NaOH}$ = 1.1220
HCl used	39.66cc.	43.37cc.	
NaOH used	20.88cc.	18.31cc.	1ccHCl = .0014651 gm N
Found nitrogen =	10.29%	10.29%	

Calculated for $C_{16}H_{12}O_2N_2$ nitrogen = 10.61%

4-Ortho-tolilido-methylene-3-phenyl-5-isoxazolon.

Equal molar quantities of di-o-totyl formamidine and

phenyl isoxazolon were heated in an oil bath at 120° for one hour. The product was crystalized out in yellow rhombic crystals, first from alcohol, then from ethyl acetate. It melts at 170°. A Kjeldahl analysis gave these results:

Substance used	.1880 gm.	Factor HCl to NaOH = 1.1220	
HCl used	41.13cc		
NaOH used	25.20cc	1ccHCl = .0014651gm nitrogen	
Found nitrogen =	10.02%		
Calculated for $C_{17}H_{14}O_2N_2$ nitrogen =	10.07%		

4-Meta-tolmido methylene-phenyl-isoxazolon.

In the same way, equal molar quantities of di-m-tolyl formamidine and phenyl isoxazolon were heated together in an oil bath at 120° for one hour. The solid mass, formed, was extracted with alcohol and a yellow compound, crystalizing from alcohol and melting at 158° was obtained. On Analized for nitrogen, the following results were obtained:

Substance	.2638gms.	.2024gms.	log Factor $\frac{HCl}{NaOH}$ = .11753
HCl used	33.42c.c.	33.19 c.c.	
NaOH used	7.91c.c	11.72 c.c.	1c.c.HCl = .0011597gm N.
Found nitrogen =	10.13%	10.22%	
Calculated for $C_{17}H_{14}O_2N_2$ nitrogen =	10.07%.		

4-Para-tolindo methylene-phenyl-isoxazolon.

Equal molar quantities of di-p-tolyl formamidine and

phenyl isoxazolon were heated for one hour at 140°. From the resulting dark colored mass, was obtained by extraction with alcohol a reddish compound, difficultly soluble in alcohol and in glacial acetic acid. Recrystalized from alcohol, it melts at 190° and, on analysis, gives these results:

Substance .2615gm. Factor $\frac{HCl}{NaOH}$ = 1.0890

HCl used 41.51 c.c.

NaOH used 18.74 c.c. 1 c.c. HCl = .0012791gm. N.

Found nitrogen = 10.32%

Calculated for $C_{17}H_{14}O_2N_2$, nitrogen = 10.07%

4-Ortho-anisido methylene-phenyl-5-isoxazolon.

Six grams of di-o-anisyl formamidine and four grams of phenyl isoxazolon were heated together at 120° for one hour. A black tar resulted. This was extracted with alcohol and from it a yellow compound was obtained. When this was purified by recrystalizing several times from alcohol it formed yellow needles which melt at 138°. Kjeldahl determinations of nitrogen were made as follows:

Substance	.2137gms.	.2119gms.	1c.c.NaOH = 1.089cc HCl
HCl used	40.93cc	47.83c.c.	1c.c.HCl = .0012791gm N
NaOH used	22.99 cc	29.35 c.c.	
Found nitrogen =	9.51%	9.59%	

Calculated for $C_{17}H_{14}O_3N_2$, nitrogen = 9.53%

4-Para-anisido methylene-3-phenyl-5-isoxazolon.

A mixture of four grams of phenyl isoxazolon and five grams of di-p-anisyl formamidine was heated for forty-five minutes at 130° in an oil bath. A difficultly soluble product was obtained by extraction with alcohol and this, when recrystalized from alcohol, gave a brown compound which melted at 168°. Nitrogen determinations follow:

Substance	.2363gms.	.2584gms.	1 c.c. NaOH = 1.089cc HCl
HCl used	41.36 c.c.	42.01 c.c.	
NaOH used	21.83 c.c.	20.87c.c.	1c.cHCl = .0012791gm:N
Found nitrogen =	9.52%	9.54%	

Calculated for $C_{17}H_{14}O_3N_2$ nitrogen = 9.53%

4-Para phenetido methylene-3-phenyl-5-isoxazolon.

Four grams of di-p-phenetdyl formamidine were heated, for one hour, at 120° with two grams of phenyl isoxazolon From the resulting oily mass a compound was crystalized out by means of alcohol, and was found to melt, when as nearly pure as possible, at 178°. Nitrogen analysis shows:

Substance	.3279 gms.	1c.c. NaOH =	1.1220cc. HCl
HCl used	63.35 c.c.	1 c.c. HCl =	.0014651 gms. N.
NaOH used	38.68c.c		
Found nitrogen =	8.91%		

Calculated for $C_{18}H_{14}O_3N_2$ nitrogen = 9.09%

4-Psendo-cumido methylene-3-phenyl-5-isoxazolon.

By heating together three grams of phenyl isoxazolon and six grams of di-psendo cumidyl formamidine, at 150° for one hour a dark mass was obtained from which alcohol separated a yellow crystaline compound. This was recrystalized from glacial acetic acid in which it is difficultly soluble and yellow needles which melt at 180° were obtained. Nitrogen analysis gave these results.

Substance .2063gms.

HCl used 41.47 c.c. 1cc NaOH = 1.089cc HCl

NaOH used 24.52 cc 1cc HCl = .0012791gm. nitrogen

Found nitrogen = 9.16%

Substance .2386gms. 1cc NaOH = 1.3108 cc HCl

HCl used 30.41 cc 1cc HCl = .0011597gm. nitrogen

NaOH used 8.56 cc.

Found nitrogen = 9.33%

Calculated for $C_{14}H_{18}O_2N_2$ nitrogen = 9.15%

4-M-nitro anilido methylene-phenyl-isoxazolon.

By heating together four grams of phenyl isoxazolon and eight grams of di-m-nitro-di-phenyl formamidines in an oil bath and crystalizing out the product from alcohol a light yellow crystaline compound, which melts at 206° was obtained. On analysis it gave the following results.

Substance .2266gm. .2026gm 1cc NaOH = 1.3108cc HCl

HCl used 39.02 cc 40.33 cc

NaOH used 9.05 cc 12.31 cc 1 cc H Cl = .0011597gm N

Found nitrogen = 13.90% 13.85%

Calculated for $C_{16}H_{11}O_4N_3$, nitrogen = 13.60%

4-Brom anilido methylene -3- phenyl-isoxazolon.

Ten grams of di-p-brom-di-phenyl formamidine and five grams of phenyl isoxazolon were heated together in an oil bath at 140° for one to two hours and a solid black mass obtained. This was washed with alcohol and recrystalized from glacial acetic acid. Brownish yellow crystals which melt at 198° were obtained. These analized as follows:

Substance	.2396gms	.2229gms	1 cc NaOH = 1.3108 cc H Cl
H Cl used	57.34 cc	46.97 cc	1 cc H Cl = .001597gm. N.
NaOH used	30.63 cc	23.46 cc	

Found nitrogen = 8.36%, 8.44%

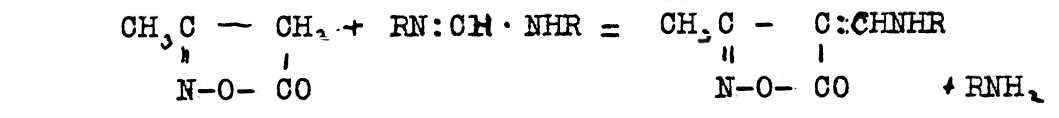
Calculated for $C_{16}H_{11}O_2N_2Br$, nitrogen = 8.16%.

METHYL ISOXAZOLON DERIVATIVES.

The amido methylene derivatives of methyl isoxazolon should be obtainable by the same methods as those of phenyl isoxazolon. There are however, two practical difficulties in carrying out these reactions. The first is that methyl isoxazolon is difficult to obtain in large enough quantities to work with; the second that it is unstable to heat and when heat enough is applied to make it react with the formamidine, the methyl isoxazolon decomposes to form a tar and, if any of the derivatives are formed by this

method, it is difficult, if not impossible, to separate them.

Unsuccessful attempts were made to obtain methyl isoxazolon by the method of Hantzsch (1), and the method of Uhlenhuth (2) was found to be not very much more satisfactory owing to the fact that the methyl isoxazolon broke down too much on heating. Better results were obtained when the oxime of acetoacetic ester was obtained as in the method of Uhlenhuth. Two grams of the oxime were then treated with concentrated ammonia water and the ammonia water distilled off under reduced pressure at 40-50°. When the volume of the mixture has come again to the original volumeof the oxime, the methyl isoxazolon is precipitated with concentrated hydrochloric acid and recrystalized from glacial acetic acid. From fourteen grams of the oxime, one and two-tenths grams of methyl isoxazolon, melting at 160° was obtained. As stated before, however, this did not react very well with the formamidines. It was, therefore, attempted to obtain these same derivatives by indirect methods. Methyl isoxazolon should react with a diformamidine, to give the amido methylene methyl isoxazolon, as follows:



Since methyl isoxazolon is made by the reaction of hydroxylamine hydrochlorid on acetoacetic ester, it was thought that it might be possible to make the amido methylene derivatives

(1)Ber. 24. 497
(2)Ann 296.46.

of methyl isoxazolon by the reaction of hydroxylamine hydrochloid on the amido methylene derivatives of aceto acetic ester. It was found, however, that by this reaction isoxazols were obtained and these will be discussed later in this paper.

It was found that these derivatives could be made without difficulty by the action of the di-substituted formamidines on benzal methyl isoxazolon(1)at the temperature at which a mixture of the two melts, the reaction being as follows:

$$CH_3C(=N.O.CO)-C:CHC_6H_5 + RN:CHNHR = CH_3C(=N.O.CO)-C:CHNHR + RN:CHC_6H_5$$

Benzal methyl isoxazolon was made in good yield by the following proceedure , a solution of fifteen grams of hydroxyl amine hydrochloride in forty cc. of water and twenty cc. of pyridine was added to a solution of twenty-five cc. of aceto acetic ester in fifty cc. of alcohol. Some heat was evolved on the addition and when the mixture had cooled for a few minutes, a solution of twenty-two cc. of benzaldehyde in one hundred and fifty cc. of 17% hydrochlorice acid was added to it and the whole allowed to stand for two days. The yellow, crystaline, precipitate of benzal methyl isoxazolon is then filtered off, washed with water and with alcohol and then dried on a drying plate. The yield is about 90%. The product is in very pretty, yellow, flakes and is pure enough to use.

(1) Ber. 28, 2733, Ber. 30, 1337.

4-Anilido methylene-3-methyl-5-isoxazolon.

Twenty grams of diphenyl formamidine was mixed with twenty grams of benzal methyl isoxazolon and the whole heated in an oil bath at 120-135° for two hours. The mixture was first heated until fusion took place and then it was allowed to cool somewhat, while the reaction continued. This was done to prevent decomposition of the isoxazolon ring, which takes place easily at higher temperatures. By this mixture a dark red mass was obtained on cooling. By extracting it with gasoline, benzal aniline melting at 54° was obtained. A second product, melting at 156°, which is soluble in KOH and re-precipitated by H Cl was obtained. It is crystalized out as a white compound and on analysis gave the following results:

Substance	.2638gms.	.2810gms.	1cc NaOH =1.0890cc. HCl
H Cl used	59.78 cc	51.21cc	1 cc HCl=.0012791gm. N.
NaOH used	29.66 cc	19.82 cc	

Found nitrogen = 13.35% 13.52%

Calculated for $C_{11}H_{10}O_2N_2$ nitrogen = 13.86%

4-O-tolnido methylene 3-methyl 5-isoxazolon.

A mixture of equal molar quantities of benzal methyl isoxazolon and di-o-tolyl formamidine was heated at 140° until it was fused. Then the temperature was allowed to fall to 120° and the heating continued for half hour at that temperature. The resulting redish mass was extracted with benzene and the com-

pound obtained was recrystalized from benzene and gasoline. A reddish compound was obtained which melts at 206°. Analysis gave these values::

Substance .2658gms 1 cc.NaOH= 1.3108 cc. H Cl.

H Cl used 32.78cc. 1 cc H Cl =.0011597gm. N.

NaOH used 2.54cc.

Found nitrogen =12. 85%

Calculated for $C_{12}H_{12}O_2N_2$, nitrogen = 12.96%

4-m-tolimido methylene-3-methyl-5-isoxazolon.

Ten grams of benzal methyl isoxazolon and ten grams of di-m-tolyl formamidine were heated together in an oil bath at 130° for one hour. The product, thus, obtained,was recrystalized from alcohol and a brownish white compound which melts at 168° was obtained. Its nitrogen analysis is given below.

Substance .3399gms. .2084gms. 1 cc.NaOH = 1.0890 cc. HCl.

HCl used 42.03 cc' 41.60cc 1 cc HCl= .001279-gm. N.

NaOH used 7.37 cc 18.69 cc

Found nitrogen = 12.83% 13.07%

Calculated for $C_{12}H_{12}O_2N_2$ nitrogen = 12.96%

4-p-tolimido methylene-3-methyl-5- isoxazolon.

When twenty grams of di-p-tolyl formamidine and eighteen grams of benzal methyl isoxazolon were heated to 130°, the mixture melted and then became semi-solid. From this mass was sep-

arated out, by the use of cold benzene a compound which, when recrystalized from alcohol in which it is difficultly soluble, gives yellow needles which melt at 204°. It is soluble in alkali and reprecipitates with acids. Nitrogen analyses are as follows:

Substance	.2847gms.	.2928gms.	1 cc.NaOH= 1.0890 cc HCl
H Cl used	46.08 cc	48.52 cc	1 cc. HCl= .0012791gm N.
NaOH used	15.12 cc.	17.05 cc	
Found nitrogen	=13.33%	13.11%	

Calculated for $C_{12}H_{12}O_2N_2$, nitrogen =12.96%

4-o-anisido methylene-3-methyl-5-isoxazolon.

An equal molecular mixture of benzal methyl isoxazolon and di-o-anisyl formamidine was heated at 140-150° for one hour. The mass which resulted was heated with alcohol and a difficultly soluble compound obtained. This was recrystalized from benzene in which it is also difficultly soluble and yellow needles which melt at 169° were obtained. Their nitrogen content is shown below.

Substance	.2778gms.	.2484gms.	1 cc.NaOH = 1.0890 cc.HCl.
HCl used	45.96 cc.	41.36 cc.	
NaOH used	18.62 cc	16.93 cc	1.cc. HCl = .0012791gms N.
Found nitrogen	= 11.85%	11.84%	

Calculated for $C_{12}H_{12}O_3N_2$, nitrogen = 12.07%.

4-p-anisido methylene-3-methyl-5-isoxazolon.

Twenty grams of di-p-anisyl formamidine and eighteen grams of benzal methyl isoxazolon were heated at 130°. From this fused

mixture two products were separated. By means of benzene, benzilidene p-anisidine was obtained. A second product, soluble in alkali, was recrystalized from alcohol and purified as a greenish yellow compound which melts at 190° and gives this nitrogen content:

Substance .2291gm. .2824gm 1cc.NaOH = 1.0890 cc. H Cl.
H Cl used 43.43 cc. 48.26 cc.
NaOH used 19.46cc. 18.70 cc. 1 cc.HCl = .0012791gm. N.
Found nitrogen = 12.31% 12.65%
Calculated for $C_{12}H_{12}O_3N_2$, mitrogen = 12.07%

4-M-xylidomethylene-3-methyl-5-isoxazolon.

A mixture of ten grams of di-m-xylil formamidine and eight grams of benzal methyl isoxazolon was heated on an oil bath at 130° for three quarters of an hour. A black oil resulted from which a solid product was separated by the addition of alcohol. This when recrystalized was nearly white and melts at 166°. It was analized for nitrogen with the following results.

Substance .2539gms. .2240gms. 1 cc.NaOH = 1.0890cc.HCl.
H Cl used 39.70cc. 41.74 cc. 1ccHCl = .0012791gm N.
NAOH used 14.99 cc. 18.34 cc
Found nitrogen 11.81% 12.46%
Calculated for $C_{13}H_{14}O_2N_2$, nitrogen = 12.18%.

4-P-phenetido methylene-3-methyl-5-isoxazolon.

When a mixture of eleven grams of di-p-phenetdyl formamidine and nine grams of benzal methyl isoxazolon was heated in

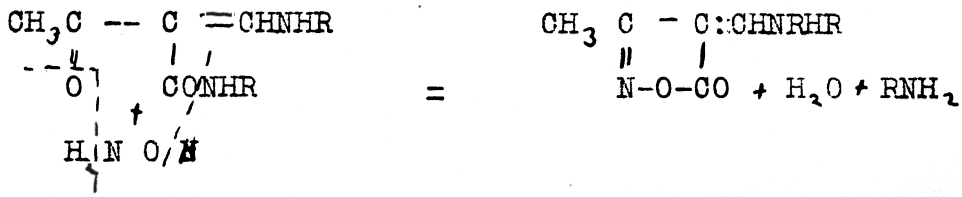
an oil bath it melted at 135° and was then heated at 120-125° for an hour. On cooling it solidified and, by recrystalizing several times from alcohol, yellow needles which melt at 169° were obtained. Benzilidene P-phenetdyn was also identified. The yellow compound was analized for nitrogen as follows.

Substance	.2151gms.	.2203gms.	1cc.NaOH = 1.3108 cc. HCl
HCl used	46.47 cc.	41.56 cc.	1cc.HCl = .0011597gm N.
NaOH used	19.02cc.	15.51 cc.	
Found nitrogen =	11.61%	11.17%	

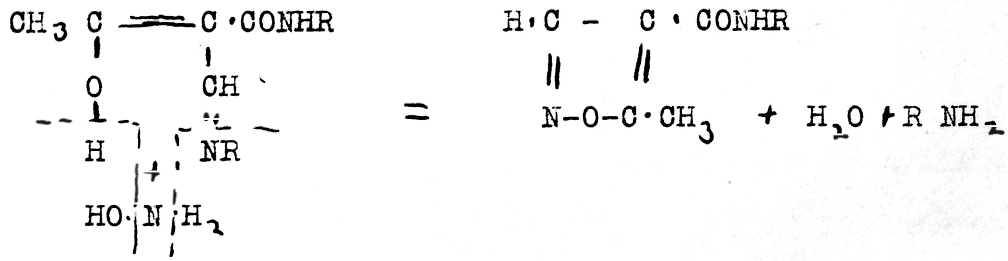
Calculated for $C_{13}H_{14}O_3N_2$, nitrogen = 11.38%

ISOXAZOL SYNTHESES.

It was mentioned on a preceeding page that an attempt was made to obtain the 4 amido methylene derivatives of-3-methyl-5-isoxazolon by the reaction of hydroxylamine hydrochloride on the amido derivatives of the amido methylene aceto acetic esters. It was thought that the reaction might take place as follows.

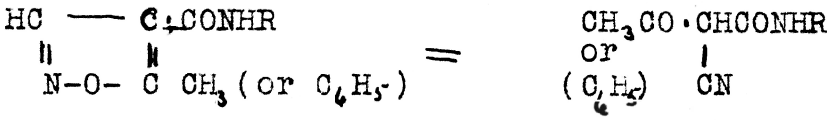


It was found, however, that this reaction does not take place. In fact, the two substances do not react to any very great extent unless the hydroxylamine hydrochloid is neutralized. If it is neutralized with pyridene the following reaction takes place.



This gives the amide of 5-methyl-4-carboxyl isoxazol. The same sort of reaction takes place when the derivatives of benzoyl acetic ester were used except that the amides of 5-phenyl 4-carboxyl isoxazol were obtained. These isoxazols are all unstable in the presence of alkalies and re-arrange to form cyan derivatives. If Na_2CO_3 is used, in place of pyridene,

to neutralize the hydroxylamine hydrochloride, no isoxazol will be obtained since it goes over directly to the cyan derivative. This cyan derivative may also be obtained by dissolving the isoxazol in sodium hydroxide solution and then precipitating with hydrochloride acid. The rearrangment is as follows:



O-toluid of 5-methyl 4-carboxyl isoxazol.

To a solution of ten grams of O-toluido methylene aceto acet o-toluid, prepared by heating together di-o-tolyl formamidine and aceto acetic ester, in alcohol was added eight grams of hydroxylamine hydrochloride, dissolved in water, and ten cc. of pyridine and the whole mixture was heated on a water bath under a reflux condenser until everything remained in solution on cooling. The alcohol was then evaporated off and water added. A white floculent precipitate of the isoxazol resulted. This was filtered off and recrystalized from benzene and from dilute alcohol. It is a white compound which melts at 112° and on analysis for nitrogen the following values were obtained.

Substance	.2072gms.	.2012gms.	1cc.NaOH = 1.3108cc.HCl
HCl used	32.25cc.	32.20cc.	1cc.HCl = .0011597gm N.
NaOH used	6.95 cc.	7.27 cc.	1

Found nitrogen = 12.95%, 13.07% - 12.97%

Calculated for $C_{12}H_{12}O_2N_2$ nitrogen = 12.97%

Acetyl cyan acet -o-toluid.

When the o-toluid of 5-methyl 4-carboxyl isoxazol was dissolved in sodium hydroxide solution and reprecipitated with hydrochloric acid, a white compound, difficultly soluble in alcohol, which melts at 110° was obtained. A mixture of this with the original isoxazol melts at 93°. This same compound was made by first making cyanacet-o-toluid by heating cyan acetic ester and o-toluidine together, at 160°, for 3-4 hours, then suspending this in dry ether and heating with an equivalent amount of metallic sodium until the sodium is dissolved, then adding considerably more than one mol of acetyl chilorid and let stand for one day. The same compound as above may then be extracted with NaOH solution and preciptated with HCl. The reaction is as follows:

$$2CNCH_2COOC_2H_5 + C_7H_7NH_2 = CNCH_2CONHC_7H_7 + C_2H_5OH$$

$$2CNCH_2CONHC_7H_7 + 2Na = 2CNCHNaCONHC_7H_7 + H_2$$

$$CNCH\cdot CONHC_7H_7 \quad + \quad Na + Cl\cdot OCCH_3 = CNCHCONHC_7H_7 \quad + \quad NaCl$$

$$\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\quad COCH_3$$

This gave the following results on analysis.

Substance	.2048gms.	.3180gms.	
HCl used	32.67 cc.	42.31cc.	1cc.NaOH = 1.3108cc.HCl
NaOH used	7.71cc.	5.39cc.	1cc.HCl = .0011597gm N.
Found nitrogen	12.78%	12.81%	
Calculated for $C_{12}H_{12}O_2N_2$ nitrogen		12.97%	

P-toluid of 5-methyl 4-carboxyl isoxazol.

Fifteen grams of p-toluido methylene aceto acet p-toluid was suspended in one hundred cc. of alcohol and to it was added a solution of twelve grams of hydroxylamine hydrochloride in water, and twelve cc. of pyridene. The mixture was heated on a water bath under a reflux condenser for four hours, until everything remained in solution on cooling. This was then diluted with water and let stand for some time in the cold. The solid which separates out was then filtered off and recrystalized from dilute alcohol. It is a white compound which melts at 140° and its nitrogen content is shown by these figures.

Substance	.2189gms.	.2026gms,	1cc.NaOH = 1.3108 cc.HCl
HCl used	4043 cc.	40.95 cc.	1cc.HCl = .0011597gm N.
NaOH used	12.10 cc.	13.93 cc.	
Found nitrogen =	13.02%	12.99%	

Calculated for $C_{12}H_{12}O_2N_2$, nitrogen = 12.97%

Acetylcyan acet p-toluid.

Some of the p-toluid of 5-methyl 4-carboxyl isoxazol obtained above was dissolved in NaOH solution and when HCl was added to the solution a white compound was precipitated. When this was recrystalized from alcohol, in which it is difficultly soluble, it was found to melt at 176°. This same compound was obtained when Na_2CO_3 was used in the preparation of the isoxazol instead of pyridine. It was also obtained by the following

method. Five grams of cyan acet p-toluid was suspended in dry ether. Two grams of sodium was added to it and the flask heated on a water bath under a reflux condenser until all the metallic sodium had disappeared. Twelve cc. of acetyl chlorid was added to it and let stand for one day. The acetyl cyan acet p-toluid was then extracted with NaOH solution and precipitated with HCl. On analysis nitrogen was shown as follows.

Substance	.2038gms.	.2113gms.	1cc.NaOH = 1.3108cc.HCl
HCl used	46.93cc.	48.10cc.	1 cc. HCl = .0011597 gm. N.
NaOH used	18.82cc.	18.92cc.	
Found nitrogen =	12.69%	12.79%	

Calculated for $C_{12}H_{12}O_2N_2$, nitrogen = 12.97%

Acetyl cyan acet anilid.

Attempts were made to obtain the anilid of 5-methyl 4-carboxyl isoxazol by the same methods as were used in obtaining the o-toluid and the p-toluid. These,were however not very successful because this isoxazol is very soluble in most solven and is therefore hard to purify. A little of it, but not enoug for anaylsis was obtained. As before, an alcoholic solution of anilido methylene aceto acetanilid was heated with NH_2OH. HCl and pyridene. This was then extracted with ether and the e ther solution was dried over fused calcium chloride and fractionally distilled under reduced (about 2 cm.) pressure. A fraction which, on cooling, became a white solid, was obtained. This

on recrystalizing from gasoline melted at 136°. On dissolving in NaOH solution and then precipitating with hCl a different white compound, which melts at 145° and which is acetyl cyan acetanilid, was obtained. This same compound is obtained when Na_2CO_3 is used above instead of pyridene. It can also be obtained by the action of sodium on cyan acetanilid and then of acetyl chlorid on the salt thus formed. Its nitrogen content is shown below.

Substance	.3110gms.	.2707gms.	1cc.NaOH = 1.0890 cc. HCl
HCl used	66.47cc.	45.25 cc.	
NaOH used	31.06 cc.	14.86 cc.	1cc. HCl = .0012791gm N.
Found nitrogen =	13.43%	13.73%	

Calculated for $C_{11}H_{10}O_2N_2$, nitrogen = 13.86%

Anilid of 5-phenyl 4-carboxyl isoxazol.

Anilido methylene benzoyl acetanilid can be obtained by heating together diphenyl formamidine and benzoyl acetic ester. By suspending this compound in alcohol and heating it with slightly more than equal molecular proportions of $NH_2OH \cdot HCl$ and pyridene, until everything remains in solution on cooling, the anilid of 5-phenyl 4-carboxyl isoxazol can be obtained and can be separated out by dilution of the alcohol with water. After recrystalizing from alcohol, it melts at 135° and gives these results on analysis.

Substance	.2162gms.	.2049gms.	1cc.NaOH = 1.0890 cc HCl
HCl used	41.30 cc.	41.42 cc.	1 cc.HCl = .0012791gm N.
NaOH used	22.30 cc.	22.01cc.	

Found nitrogen = 10.08% 10.91%

Calculated for $C_{16}H_{12}O_2N_2$, nitrogen = 10.61%

Benzoyl cyan acetanilid.

When the anilid of 5-phenyl 4-carboxyl isoxazol was dissolved in NaOH solution and reprecipitated by the use of HCl, a different compound, which when recrystalized from alcohol, melts at 203°, was obtained. The same compound was obtained by the action of benzoyl chlorid on cyan acetanilid in pyridene solution. No analysis was obtained of it but it was very probably benzoyl cyan acetanilid.

O-tolnid of 5-phenyl 4-carboxyl isoxazol.

O-tolnido methylene benzoyl acet o-tolnid was made by heating together di-o-tolyl formamidine and benzoyl acetic ester. Some of it was then suspended in alcohol and to it was added some -what more than equal molecular amounts of NH_2OH HCl dissolved in water, and pyridene. The mixture was boiled on a water bath under a reflux condenser until it all went in to solution. Then the isoxazol was precipitated by dilution with water and recrystalized from alcohol. It is white and melts at 114°. Analysis shows,

Substance	.2186gms	.2490gms.	1cc.NaOH = 1.3108cc.HCl
HCl used	28.82cc.	32.24cc.	
NaOH used	7.08cc.	7.83cc.	1cc.HCl = .0011597gm N
Found nitrogen =	10.37%	10.24%	

Calculated for $C_{17}H_{14}O_2N_2$, nitrogen = 10.07%

Benzoyl cyan acet o-toluid.

Some of the o-toluid of 5-phenyl 4-carboxyl isoxazol was dissolved in NaOH and reprecipitated with HCl. This compound, when recrystalized from alcohol was white and melted at 132°. Analysis shows the following:

Substance	.2684gms.	.2444gms.	1cc.NaOH = 1.0890cc HCl
HCl used	41,20cc.	40.66cc.	1ccHCl = .0012791gm.N.
NaOH used	18.18cc.	18.97cc.	
Found nitrogen =	10.20%	10.47%	

Calculated for $C_{17}H_{14}O_2N_2$, nitrogen = 10.07%

This same compound was made by heating o-toluido methylene benzoyl acet o-toluid suspended in alcohol with $NH_2OH \cdot HCl$ and Na_2CO_3. It was then extracted with NaOH solution and recrystalized.

P-toluid of 5-phenyl 4-carboxyl isoxazol.

Benzoyl acetic ester and di p-tolyl formamidine when heated together at 150° give p-toluido methylene benzoyl acet p-toluid in good yield. Twenty-two grams of this was suspended in about 100cc of alcohol and a water solution of some-what more than molecular amounts of hydroxylamine and pyridene was added.

The whole was boiled on a water bath under a reflux condenser until everything remained in solution on cooling. By dilution with water a white compound was obtained. This crystalizes out from alcohol and melts at 158°. Analysis shows the following:

Substance	.2064gms	.5133gms	1ccNaOH = 1.3108cc HCl.
HCl used	47.07cc.	60.16cc.	1cc.HCl = .0011597gm.N
NaOH used	22.52cc.	11.41cc	
Found nitrogen =	9.86%	10.21%	

Calculated for $C_{17}H_{14}O_2N_2$, nitrogen = 10.07%

Benzoyl cyan acet p-toluid.

P-toluido methylene benzoyl acet p-toluid was treated as above for the isoxazol except that Na_2CO_3 was used in place of pyridene and the resulting solution was extracted with NaOH solution. By this method on precipitation with HCl a white crystaline compound was obtained. By recrystalizing from alcohol it was purified and was then found to melt at 180°. This same compound was obtained by dissolving the p-toluid of 5-phenyl 4-carboxyl isoxazol in NaOH and then acidifying with HCl. It was also gotten by treating cyan acet p-toluid in benzene, with sodium and with benzoyl chlorid, then extracting with NaOH. It was analized with these results.

Substance	.2572gms.	.2358gms	1cc.NaOH = 1.0890cc.HCl
HCl used	42.69cc.	42.48cc.	
NaOH used	20.28cc.	22.36cc.	1ccHCl = .0012791gm N.
Found nitrogen =	10.24%	9.83%	

Calculated for $C_{17}H_{14}O_2N_2$, nitrogen = 10.07%

P-anisido methylene benzoyl acet p-anisidid.

Molar quantities of di p-anisyl formamidine and benzoyl acetic ester were heated together on an oil bath at 140° for one hour. The product which was obtained was boiled out with alcohol and recrystalized from benzene. It was in yellow crystals which melt at 196° and show the following amounts of nitrogen.

Substance	.2804gms	.2714gms	1ccNaOH = 1.3108cc HCl
HCl used	46.43cc	35.52cc.	1cc.HCl = .0011597gm.N
NaOH used	22.30cc	14.58cc	

Found nitrogen = 7.11% 7.01%,

Calculated for $C_{24}H_{22}O_4N_2$ nitrogen = 6.97%

Banisidid of phenyl 4-carboxyl isoxazol.

Molar quantities of the p-anisyl methylene benzoyl acet p-anisidid, obtained above, and hydroxylamine hydrocholride and pyridene in alcohol were boiled on a water bath under a reflux condenser until everything remains in solution on cooling. Then precipitated the isoxazol by adding water and recrystalize from alcohol. It is a white compound which melts at 142° and was found to contain nitrogen in the amounts shown.

Substance	.2558gms.	.2055gms	1ccNaOH = 1.3108cc.HCl
HCl used	31.35cc.	31.25cc.	1cc.HCl = .0011597gm N.
NaOH used	7.31cc.	10.50cc	

Found nitrogen = 9,87% 9.87%

Calculated for $C_{17}H_{14}O_3N_2$ nitrogen = 9.53%

Benzoyl cyan acet p-anisidid.

The above p-anisidid of 5-phenyl 4-carboxyl isoxazol was dissolved in KOH and on acidifying with HCl a white product was obtained which was difficultly soluble in alcohol. When recrystalized from glacial acetic acid it melts at 194°. It was analized with the following results.

Substance	.2125gms.	2804gms	1cc.NaOH = 1.3108ccHCl
HCl used	3089cc	31.42cc	1cc.HCl = .0011597gm N.
NaOH used	9.76cc.	6.51cc	

Found nitrogen = 9.88% 9.47%

Calculated for $C_{17}H_{14}O_3N_2$ nitrogen = 9.53%.

Aceto Acetic-ester Derivatives.

As is stated in a paper by Dr. Dains acetoacetic ester reacts in two ways with the disubstituted formamidines as follows.

$$CH_3CO\cdot CH_2COOC_2H_5 + RNCHNHR = CH_3CO\cdot \underset{\underset{CH\cdot NHR}{\|}}{C}\cdot COOC_2H_5 + RNH_2$$

$$RNH_2 + CH_3COC\cdot COOC_2H_5 = CH_3COC\underset{\underset{CHNHR}{\|}}{C}CONHR + C_2H_5OH.$$

Some new compounds of these types were made and their descriptions will be given below.

O-anisyl methylene aceto acetic ester.

Twenty grams of di o-anisyl formamidine and twenty grams of aceto acetic ester were heated on an oil bath at 125° for an hour. A product was obtained which was very soluble in alcohol benzene and gasoline. It was recrystalized from gasoline and found to melt at 107°. It was analized for nitrogen with the following results.

Nitrogen = 5.86% 5.50%

Calculated for $CH_3COC\underset{\underset{CHNHC_6H_4OCH_3}{\|}}{C}COOC_2H_5$ - $C_{14}H_{17}O_4N$.

Nitrogen = 5.32%

M-xylidomethylenea-ceto a cetic ester.

Equal molar quantities of di m-xylil formamidine and of aceto acetic ester were heated together on an oil bath at about 120° From this mass was obtained a white crystaline

compound which melts at 122°. It was analized for nitrogen with the following results:

Substance	.2093gms	.2022gms.	1cc.NaOH = 1.3108cc. HCl
HCl used	20.73cc.	21.15cc.	1cc.HCl = .0011597gm. N.
NaOH used	8.02cc.	8.58cc	

Found nitrogen = 5.66% 56.8%

Calculated for $C_{15}H_{18}O_3N$, nitrogen = 5.39%

O-phenetido methylene aceto acetic ester.

Di-o-phenetdyl formamidine was heated with aceto acetic ester in equal molecular quantities on an oil bath at 120° for one hour. A white product was obtained by recrystalizing from gasoline. It melts, when pure, at 111° and shows the following nitrogen content.

Found nitrogen = 4.75% 4.84%

Calculated for $C_{13}H_{17}O_4N$ nitrogen = 5.06%

P-tolnido methylene benzoyl acetic ester.

By heating together di-p-tolyl formamidine and benzoyl acetic ester on an oil bath and extracting the product with gasoline, a product was obtained which recrystalized from gasoline in fine yellow flakes and melts at 98°. It gave analyses which do not agree very well with what was expected but agree well with themselves and do not change on recrystalizing. The results are shown below:

Substance .2506gms. .2431gms. .2631gms. .2620gms.

HCl used 25.95cc. 26.13cc. 21.12cc 20.51cc

NaOH used 11.71cc 11.79cc. 7.49cc 7.12cc.

1cc NaOH = 1.3108cc HCl

1cc HCl = .0011597gms N.

Found nitrogen = 4.91% 5.09% 4.98% 4.95%

Calculated for $C_{17}H_{19}O_3N$, nitrogen = 4.53%

AMIDES OF CYAN ACETIC ESTES.

It is well known that cyan acetic ester reacts with amines to form substituted cyan acetamides. Thus with aniline cyan acetanilid is formed the general reaction being as follows:

$$CNCH_2COOC_2H_5 + HNHR = CNCH_2CONHR + C_2H_5OH$$

In carrying out other experiments two of these derivatives were obtained which are not recorded in literature and will therefore be given.

Cyan acet m-toluid.

Molar amounts of cyan acetic ester and m-toluidine were heated together at 160° for several hours. This was then cooled, washed with dilute hydrochloric acid, and recrystalized from benzene. It is a white compound which melts at 138°. Its nitrogen content is shown below.

Substance .2128gms 1cc.NaOH = 1.3108ccHCl

HCl used 40.47cc. 1ccHCl = .0011597gm.nitrogen

NaOH used 8.19cc

Found nitrogen = 16.20%

Calculated for $C_{10}H_{10}ON_2$ nitrogen = 16.09%

Cyan acet p-anisidid

By heating molar amounts of cyan acetic ester and p-anisidine at 160° for several hours a reaction took place and a white compound melting at 138° could be obtained.
This gave the following analyses:

Substance	.2202gms.	0.2293gms	1cc. NaOH = 1.3108cc HCl
HCl used	40.56cc	36.88cc.	
NaOH used	9.34cc.	5.61cc.	1cc.HCl = .0011597gms. N
Found nitrogen =	14.91%	14.94%	

Calculated for $C_{11}H_{10}O_2N_2$ nitrogen = 14.74%